EFFECTS OF THE ADMINISTRATION OF 5-HYDROXY-DL-TRYPTOPHAN AND 3,4-DIHYDROXYPHENYLALANINE ON THE ACQUISITION OF A CONDITIONED AVOIDANCE RESPONSE

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An abstract of a thesis by
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The administration of 3,4-dihydroxyphenylalanine (L-Dopa) has been shown to result in the facilitation of performance while the administration of 5-hydroxytryptophan (5-HTP) results in an impairment of performance and reported enhancement of acquisition. The purpose of the present study is to compare the effects of 5-HTP and L-Dopa on the acquisition of a single behavioral task.

Each animal received a total of twenty daily trials in a shuttle box one hour after injection. All mice learned to avoid footshock both during each trial and the inter-trial interval. The results indicate that 5-HTP and L-Dopa do not facilitate the acquisition of a conditioned avoidance task. A significant number of inter-trial cross-overs was obtained for the L-Dopa group for the 13 days of training and the 5-HTP group for the first 2 days.

It was concluded that possible peripheral effects of L-Dopa interfered with acquisition. It was suggested that the effects of 5-HTP upon the visual system might have served to inhibit acquisition of a visual task. In view of the subject x treatment interaction, it would appear that the metabolites of 5-HTP and L-Dopa produced effects which varied within subjects as a function of the daily administration of precursors.

The further analysis of effects of 5-HTP and L-Dopa on acquisition should include correlations between variations in regional concentrations and specific behaviors.

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CHAPTER I

INTRODUCTION

Through the use of behavioral and biochemical methodologies, the role of the monoamines in the study of brain function as well as the chemotherapy of behavior disorders has been the focus of much interest (Himwich & Schade, 1965). Currently, the study of the effects of monoaminergic neurotransmitters provides a basis for much of the work undertaken in the area of psychopharmacology. An analysis of the behavioral effects of increased brain levels of 5-hydroxytryptamine (5-HT) and dopamine (DA) often serve as a preliminary tool for the evaluation of these drug effects. However, investigations of the effects of various levels of brain 5-HT and DA upon animal behavior have resulted in a wide variety of conflicting reports.

Brain levels of biogenic amines such as 5-HT, a proposed central nervous system (CNS) neurotransmitter (Eidusen, Geller, Yuwiler & Eiduson, 1964; Valzelli, 1973), and DA, which is necessary for the production of norepinephrine (NE), have been shown to be elevated by the administration of their respective precursors, 5-hydroxytryptophan (5-HTP) and 3,4-dihydroxyphenylalanine (L-Dopa). While the administration of 5-HTP results in increased brain levels of 5-HT (Green & Sawyer, 1964), it is also reported that brain levels of NE increase (Okada, Saito, Fujieda & Yamashita, 1972). As a result of precursor loading for DA there is an increase of DA

and NE (Kellogg & Lundborg, 1972) as well as a concomitant decrease of 5-HT in mice (Everett & Borcherding, 1970).

Utilizing the technique of precursor loading, much research with animals has been done with respect to performance on a given task. Aprison and Ferster (1961a, 1961b) have demonstrated a disruption of pecking behavior in pigeons resulting from the administration of 5-HTP (25, 50 and 75 mg/kg). A concomitant temporal relationship between decreased performance and 5-HT concentrations in the diencephalic and telencephalic regions of the brain of the pigeon as a result of the administration of 50 mg/kg of 5-HTP was also reported (Aprison, Wolf, Poulos & Folkerth, 1962). Other studies have demonstrated that increased brain levels of 5-HT can impair the ability of cats to perform in a conditioned avoidance situation in order to avoid foot shock (McGeer, P. L., Wada, & McGeer, E. G., 1963b) and results in a deleterious effect on performance in a conditioned avoidance situation when a shuttle response to auditory stimuli is required (Wada, Wrinch, Hill & McGeer, 1963).

On the other hand, reports of the effects of decreased levels of brain 5-HT have produced a variety of effects which appear to vary with the particular methodology employed. Some of the behavioral effects of para-chlorophenylalanine (PCPA), a reported specific depletor of brain 5-HT (Koe & Weissman, 1966), are an enhancement of acquisition of the active avoidance response at low shock intensities but not at higher shock

intensities (Tenen, 1967); facilitation of acquisition of brightness discrimination in water deprived and satiated rats (Stevens, 1970); an enhancement of performance in conditioned avoidance situations for single injections and retardation by chronic treatment (Schlesinger & Schreiber, 1968); retardation of simultaneous brightness and simultaneous pattern discrimination (Fifer[1], Yuwiler & Geller); and no difference upon food rewarded maze performance (McFarlain & Bloom, 1972).

Recent studies would indicate that the behavioral effects of PCPA may be the result of nonspecific effects upon brain biogenic amines. PCPA (300 mg/kg) has been shown to lower the NE content of rat brain by 81 percent of that of controls 2 hours after injection and 84 percent of controls after 24 hours (Peters, Filczewski & Mazurkiewicz-Kwilecki, 1972). The nonspecificity of PCPA in relation to the depletion of 5-HT may provide a possible explanation for conflicting behavioral reports. Stark and Fuller (1972) suggest that the effect of PCPA is to lower the brain levels of the catecholamines and 5-HT as a result of a PCPA metabolite which inhibits tyrosine hydroxylase and tryptophan hydroxylase.

The effects of increased or decreased catecholamine levels within the brain tend to reflect a more consistent effect upon the performance of the tasks investigated. It has been demonstrated that a facilitation of performance

[1] Unpublished study entitled "Retardation of visual Discrimination Learning in the Rat by Para-Chlorophenylalanine," 1965. Now at Drake University, Des Moines, Iowa 50311.

upon a shuttle task in conjunction with a marked decrease in the mean latency of the avoidance response can occur as a result of the administration of 20-50 mg/kg of L-Dopa (Wada et al., 1963). On the other hand, the use of alpha-methyl-tyrosine (α-MT), an inhibitor of tyrosine hydroxylase, the enzyme that limits the formation of L-Dopa and eventually DA and NE, has produced a disruption of avoidance behavior in cats on a conditioned avoidance task in a shuttle box (Hanson, 1965). Hanson also found that such disruptive effects of α-MT were completely reversed by the administration of 7.5 and 10 mg/kg of L-Dopa given 15 hours after α-MT.

These studies appear to be far from conclusive, however. Evidence suggests that behavioral deficits due to the administration of α-MT may be directly related to the rate of α-MT-produced brain-catecholamine depletion. While it was found that 200 mg/kg of peroral α-MT or multiple intraperitoneal injections of 150 mg/kg of α-MT did impair the performance of rats in a shuttle box (Rech, Borys & Moore, 1966), it was suggested that the effects of higher dosages of α-MT (200-300 mg/kg) were due to the toxicity of α-MT. It is a distinct possibility that the disruption of the behavioral responses could be secondary to the toxic effects of α-MT on organ systems other than the CNS (Rech et al., 1966; King, 1971).

Examination of the effects of monoamine precursors and/or depletors on the acquisition of a behavioral response

often reveals sharp contrasts to studies of performance where the response has already been acquired prior to drug administration. For example, α-MT (100 mg/kg, ip) given 0-8 hours before a 1-trial passive avoidance task for mice resulted in impaired avoidance acquisition (Essman, 1971). Yet, the depletion of brain NE by 6-hydroxydopamine (6-OHDA) in rats resulted in a significant increase in the rate of avoidance acquisition (Cooper, Breese, Howard & Grant, 1972). In this study, Cooper et al. (1972) also reported that there was no difference in the number of avoidance responses made by rats that were depleted of DA, nor did rats reportedly depleted of both DA and NE show any evidence of acquisition when compared to controls on a shuttle task.

Administration of 5-HTP has been shown to facilitate the acquisition of a visual discrimination. It has been shown that increased brain levels of 5-HT can facilitate a visual discrimination as a consequence of the dosage level of 5-HTP (Fifer[2] & Whitehouse). In this study, the lowest dose of 5-HTP (25 mg/kg, ip) resulted in a stimulus-dependent retardation effect when rats were trained to a simultaneous brightness discrimination task. Earlier studies have shown that a drug-mediated elevation of brain 5-HT can result in a reduction of learning efficiency in mice when the apparent source of motivation is the opportunity to hide from view in a T-

[2]Unpublished study entitled "Facilitation of Visual Discrimination Learning in the Rat by Increases in Brain 5-Hydroxytryptophan," 1972.

maze (Woolley & Van Der Hoeven, 1963). In this study acquisition was impaired with 60 mg/kg of 5-HTP but the administration of 300 mg/kg of 5-HTP further reduced learning efficiency.

Essman (1971) reported a decrement in the acquisition of a 1-trial passive avoidance response in mice that was dependent upon the level of foot shock used. Weaker shock levels (3.0 mA) produced a 25 percent reduction and higher shock levels (6.0 mA) a 10 percent reduction in acquisition.

Recent attempts have been made to demonstrate the importance of biogenic amines in the formation of long-term memory. It was reported that the lowering of brain NE content without concomitant DA depletion by the intraperitoneal administration of a nonspecific depressor of brain monoamine levels, reserpine, immediately after training interfered with the acquisition of a shuttle response while the administration of L-Dopa (100 mg/kg, ip), 5-HTP (200 mg/kg, ip), and PCPA (316 mg/kg, ip) after training did not have any effect upon memory (Dismukes & Rake, 1972). In another study by Rake (1973) it was reported that reserpine (3.0 mg/kg, ip) and L-Dopa (100 mg/kg, ip) or reserpine (3.0 mg/kg, ip) and 5-HTP (200 mg/kg, ip) administered immediately after training of a step-through response enhanced acquisition.

However, these designs fail to consider the time necessary for the precursors or depletors of brain amines to cross the blood-brain-barrier. The intraperitoneal administration

of any drug for the purpose of enhancing or disrupting the memory trace is not congruent with the consolidation hypothesis thereby suggesting that the consolidation of a memory trace takes place within a short period of time after the learning experience. Because of the possible peripheral actions of reserpine, L-Dopa or 5-HTP, one cannot be certain whether the central effects of these drugs or an alteration of afferent nervous activity were responsible for the effect upon acquisition. In fact, reserpine administered alone may cause a massive release of amines during the early stages of its action.

The physiological effects of increased brain levels of 5-HT or DA have been described primarily in terms of their behavioral effects. But such studies often times fail to consider the interaction effects of each of these amines upon the uptake, storage, and metabolism of the other neurohormone. The implications that 5-HT is an effective <u>in vitro</u> inhibitor of the enzymatic and auto-oxidation of DA and NE (Vander Wende & Johnson, 1970; Hartley & Smith, 1972) coupled with the fact that serotonergic nerve cell bodies and possibly serotonergic nerve terminals have the capacity to take up and concentrate catecholamines (Barrett & Balch, 1971) make it especially difficult to assess behavioral effects of precursor loading of 5-HTP and L-Dopa.

It has been suggested that a barrier for L-Dopa and 5-HTP exists at the capillary level in the form of an enzymatic

"trapping mechanism" (Hillarp, Fuxe & Dahlstrom, 1966). The possibility that dopa decarboxylase and monoamine oxidase are present in the walls of cerebral capillaries may be indicative of the degree of competition between the amine precursors for penetration into the brain. Such a barrier in combination with metabolic turnover as the mechanism for depletion of cerebral 5-HT following L-Dopa administration (Barrett & Balch, 1971) could provide a possible explanation for the variety of results obtained by behavioral studies.

It is interesting to note that McGeer, P. L., McGeer, E. G. & Wada (1963a) found that the administration of L-Dopa (30 mg/kg, ip) resulted in an increase of DA and NE as well as a decrease of brain 5-HT. The converse effect was obtained with 30 mg/kg of 5-HTP. There was a large increase in 5-HT accompanied by a decrease in catecholamines. This competition is further emphasized by data obtained by Wada et al. (1963). The administration of 5-HT to cats resulted in a deleterious effect on performance in a shuttle box but the administration of L-Dopa resulted in an improvement in performance. A most striking effect was obtained in studies where L-Dopa and 5-HTP were administered together. It was found that performance depended not upon the absolute level of catecholamines or 5-HT present in the brain but rather on the balance between the catecholamines and 5-HT (Wada et al., 1963).

No studies have been found in which the effects of increased brain levels of 5-HT and DA are directly compared with

respect to the acquisition of a particular behavioral task within the same study. This lack of comparative data makes it difficult to assess the significance of studies indicating that 5-HT and DA concentrations influence the uptake, storage and metabolism of each other. Studies by McGeer et al. (1963 a) of the effects of brain amine levels on performance support biochemical and histological evidence of an interaction between 5-HT and DA. Other studies, previously mentioned, of the effects of 5-HTP and L-Dopa on performance and acquisition suggest the importance of these amine precursors in a learning situation. In view of the wide range of effects of 5-HT and DA precursors and/or depletors upon performance and learning, the purpose of the present study is to compare the effects of precursor loading of 5-HTP and L-Dopa on the acquisition of a conditioned avoidance response.

Secondary to a comparison of the effects of 5-HTP and L-Dopa on the acquisition of the same task, the present study attempted to demonstrate the ability of these amine precursors to facilitate the acquisition of a visual discrimination. Since the effects of increased brain levels of 5-HT reportedly result in behavioral deficits and/or performance decrements and L-Dopa produces a general increase in activity level, it would seem reasonable to expect that these effects, whether central, peripheral, or the result of a biochemical interaction, can serve to be operative upon the acquisition of a conditioned avoidance response.

CHAPTER II

METHOD

Subjects

Twenty-four male Swiss Webster albino mice, obtained from Blue Spruce Farms, Altamont, New York were used. The Ss, approximately 65 days old, were housed two to a cage for 7 days prior to training. Each animal received food and water ad lib throughout the study.

Apparatus

The apparatus was a 45 x 16.25 x 17.50 cm. shuttle box constructed of clear Plexiglas. The grid floor consisted of 0.31 cm. brass rods spaced 1.0 cm. apart on centers. Foot shock, supplied by a constant current source at 0.5-ma, was scrambled by a Davis Shock Scrambler (Davis Co., California). A barrier of black Plexiglas with a 3.75 cm. dia. hole through its center was placed between the two chambers. The conditioned stimulus (CS) was two 12-v lamps (Chicago, CM-1816) wired in parallel which comprised a single light source. The CS was located 10 cm. above the grid floor between the two compartments. A 4.38 cm. opal glass lens was at a 45° angle to each side of the apparatus. Latencies were recorded by a Standard Electric clock that was activated at the onset of each trial and terminated when the respective photorelay was tripped as the animal entered the safe chamber. During the inter-trial interval, foot shock was always available to one side of the apparatus in order to discourage

inter-trial crossovers. Ambient light was supplied by a 7-w red bulb. The shuttle box was placed in a sound attenuated room and, except for the shock scrambler, all electronic equipment and relays were located in an adjacent room.

Procedure

Each animal was randomly assigned to one of three groups. Group 1 and group 2 received 50 mg/kg of 5-hydroxy-DL-tryptophan (5-HTP) and 100 mg/kg of 3,4-dihydroxyphenylalanine (L-Dopa), respectively. 5-HTP and L-Dopa were dissolved in 0.10 N hydrochloric acid and the pH was adjusted to approximately 7.40 with 10 N sodium hydroxide in 0.10 N hydrochloric acid. Group 3, the vehicle control, was administered the vehicle used to prepare the drugs for injection. All injections were given intraperitonealy and were of equal volume, e.g., 0.50 cc per injection. Solutions containing the drugs were prepared on a daily basis.

All Ss received drug injections daily one hour prior to training. Each S received a total of twenty trials daily. The Ss were run by groups with the sequence of the groups varying randomly each day. The onset of the CS signaled the start of each trial. Foot shock was delivered 10-sec. after the onset of the CS and remained on until the S crossed over to the other side of the apparatus. If S responded with a latency of less than 10-sec., the response was defined as an avoidance. If the latency exceeded 10-sec., the response was defined as an escape. The Ss were placed alternately in

either the right or left side of the apparatus at the beginning of each block of trials. The inter-trial interval varied randomly from 10-sec. to 30-sec. with a mean of 20-sec. The CS terminated with each successful avoidance or escape. Training was terminated when all three groups had attained a level of 80 percent correct responding on the thirteenth day of training.

CHAPTER III

RESULTS

At no time did any of the animals show signs of ataxia or diarrhea following the injections of 5-HTP, L-Dopa or the vehicle. Nor were there any differences in the mean body weight between the groups. It did, however, become obvious after the third day of training that the L-Dopa group was more sensitive to handling than the other two groups. This hypersensitivity persisted throughout the remainder of the study.

Mean latencies for all groups are shown in Figure 1. A two-way analysis of variance with repeated measures performed on the latency of the response for 13 days of training resulted in a nonsignificant drug effect ($F = 1.48$, $df = 2/21$, $P > .05$). Analysis of the latency of response for the first 6 days of training revealed a significant drug effect ($F = 4.44$, $df = 2/21$, $P < .05$). Subsequent analysis of the drug effect by the Tukey test showed no difference for L-Dopa vs Control ($q = 1.37$, $df = 1/42$, $P > .05$), 5-HTP vs Control ($q = 0.47$, $df = 1/42$, $P > .05$), and L-Dopa vs 5-HTP ($q = 0.87$, $df = 1/42$, $P > .05$). The test for homogeniety of variance assumption is valid for latencies ($C = 0.4828$). Computation of the omega coefficient for latencies for the first 6 days accounts for 26 percent of the variance for the drug effect ($w^2 = 0.26$).

A two-way analysis of variance with repeated measures performed on the percent of avoidance resulted in a nonsig-

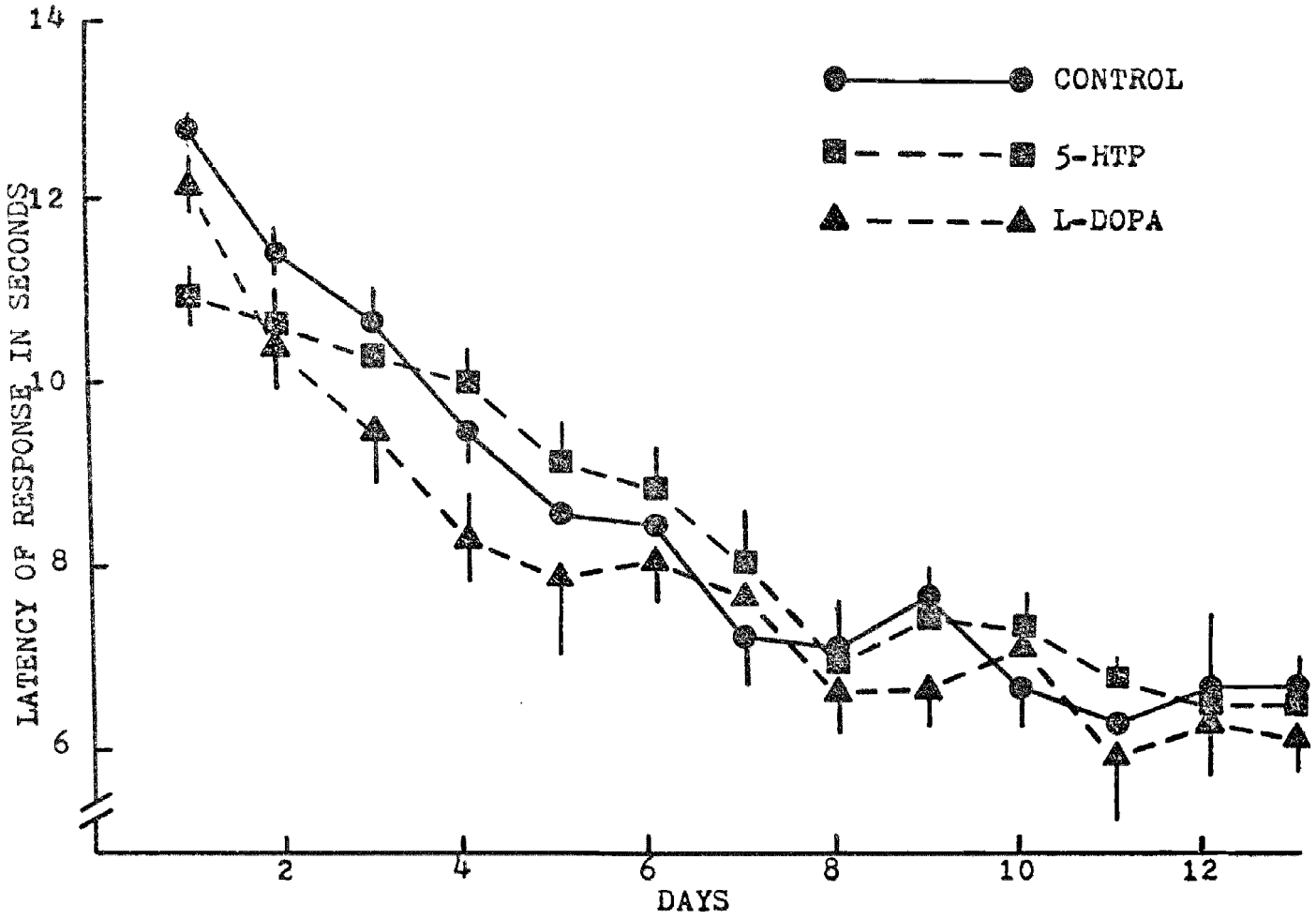

Figure 1. The effect of 5-HTP and L-Dopa on response latency. Each value represents the mean ± S.E.M. for each group. There is no difference between any of the groups ($P > .05$).

nificant drug effect for 13 days of training (F = 0.74, df = 2/21, $P > .05$) and the first 6 days of training (F = 0.75, df = 2/21, $P > .05$). As can be seen in Figure 2, daily training sessions for 13 days were highly effective (F = 129.37, df = 12/252, $P < .001$). There was a drug x trials interaction for 13 days of training (F = 1.60, df = 24/252, $P < .05$) and the first 6 days of training (F = 5.94, df = 10/105, $P < .001$). The test for homogeniety of variance assumption is valid for the avoidance measure (C = 0.3828) and the drug by trials interaction accounts for 65 percent of the variance for the first 6 days of training (w^2 = 0.65).

A two-way analysis of variance with repeated measures performed on the frequency of inter-trial crossovers indicates a significant drug effect for 13 days (F = 17.72, df = 2/21, $P < .001$). As can be seen in Figure 3, the L-Dopa group had significantly more crossovers than the 5-HTP group (q = 14.59, df = 2/21, $P < .01$) and the Control group (q = 17.15, df = 2/21, $P < .01$). There was no difference between the 5-HTP and Control groups (q = 2.56, df = 2/21, $P > .05$). The test for homogeniety of variance assumption is valid for crossovers (C = 0.5912) and computation of the omega coefficient indicates that the drug effect accounts for 60 percent of the variance (w^2 = 0.60).

The Duncan New Multiple Range Test performed on the first 2 days of training indicates that the 5-HTP group produced significantly more crossovers than the Control group

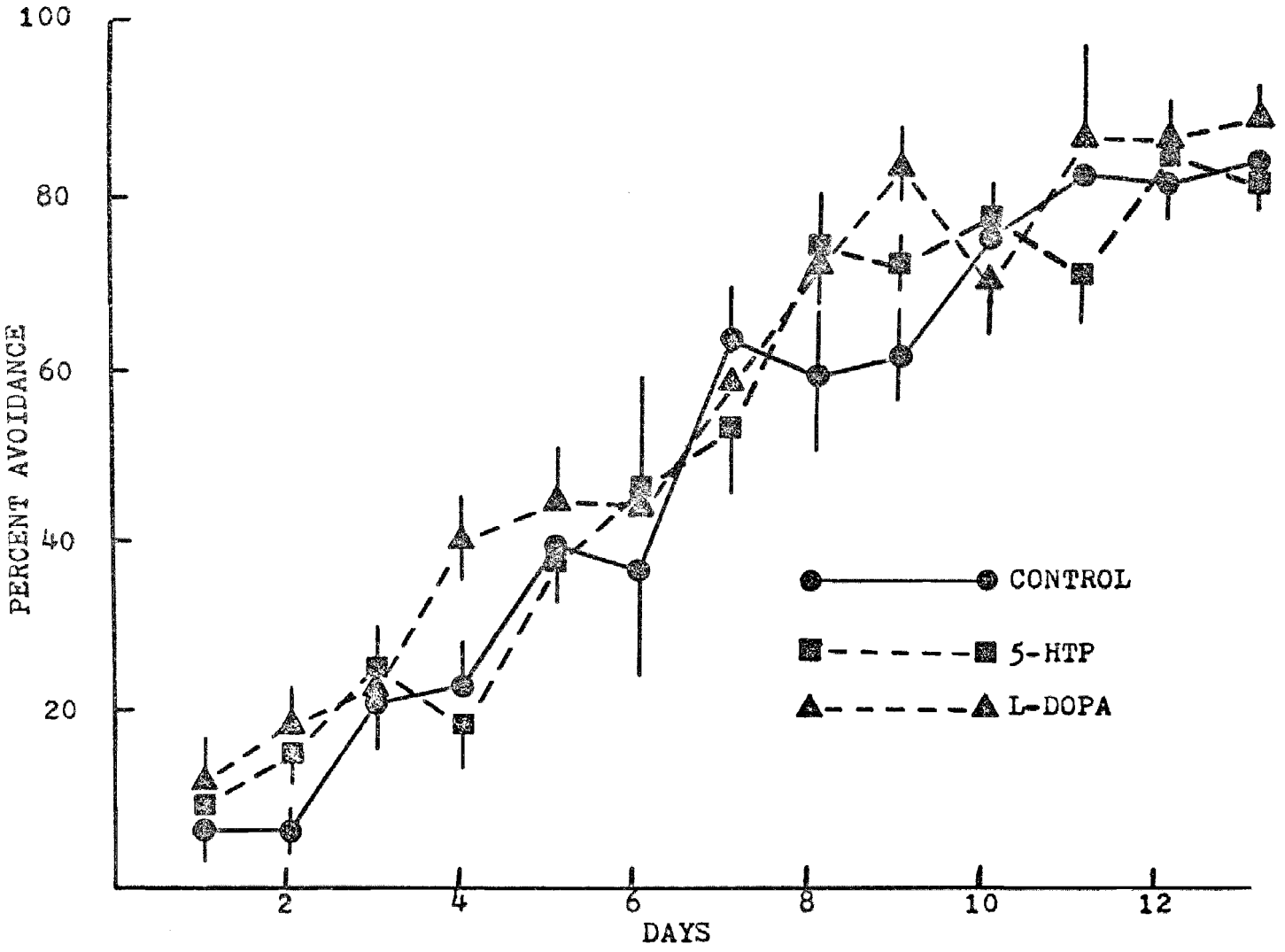

Figure 2. The effect of 5-HTP and L-Dopa on avoidance probability. Each vaule represents the mean ± S.E.M. for each group. There is no difference between any of the groups ($\underline{P} > .05$).

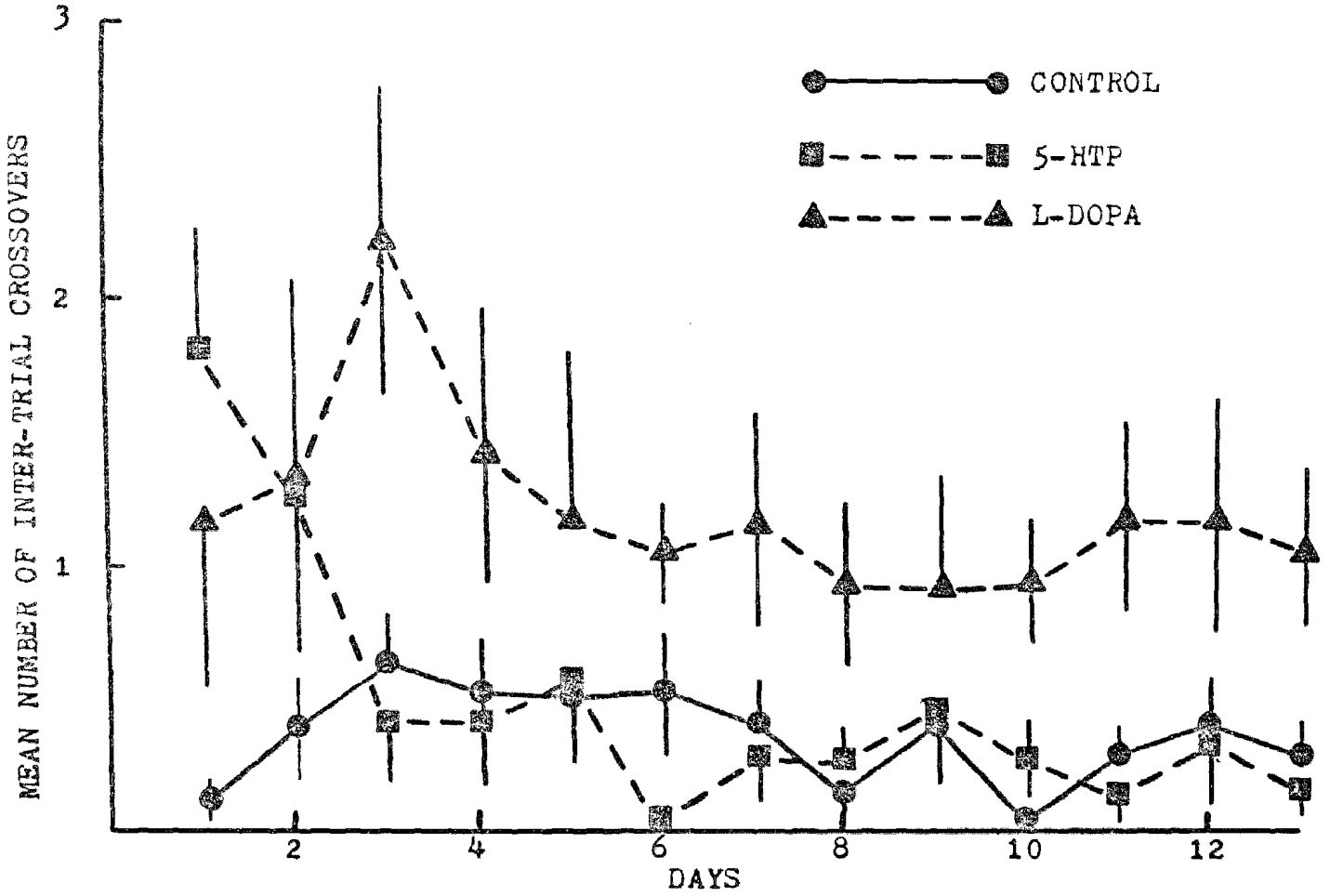

Figure 3. The effect of 5-HTP and L-Dopa on inter-trial crossovers. Each value represents the mean ± S.E.M. for each group. The L-Dopa group is significantly different from the 5-HTP group ($P < .01$) and Controls ($P < .01$). The 5-HTP group is significantly different from the Controls on day 1 ($P < .005$) and on day 2 ($P < .05$).

on day 1 ($P < .005$) and day 2 ($P < .05$). There was no difference between the L-Dopa and 5-HTP groups for either day 1 or day 2 ($P > .05$).

CHAPTER IV

DISCUSSION

The results of the present study indicate that the administration of 5-HTP (50 mg/kg) or L-Dopa (100 mg/kg) does not facilitate the acquisition of a conditioned avoidance response. Analysis of the percent of avoidances for the first six days revealed a subject by treatment interaction. After the third day of training the L-Dopa group was more sensitive to handling than any other group. The 5-HTP group showed a significant decrease in the number of inter-trial crossovers during the first two days of training.

The finding that 5-HTP did not facilitate acquisition as measured by latency and percent of avoidances does not agree with studies suggesting that the administration of 5-HTP enhances learning; nor does it coincide with studies demonstrating a decrement in learning or performance. Though the present study does not permit an analysis of peripheral drug effects, the results do not appear to be influenced by the effects of precursor loading of 5-HTP on activity level and mobility. Studies of the effects of small doses of 5-HTP (6.25-50 mg/kg, ip) administered to male albino mice have shown that spontaneous activity was not affected (Modigh, 1972; 1973).

Increased brain levels of DA have been reported to result in an increase of spontaneous motor activity (Eiduson et al., 1964; Kellogg & Lundborg, 1972; Geyer, Segal &

Mandell, 1972) and agressiveness (Lycke, Modigh & Roos, 1969). It seems likely that a change in motor activity due to the conversion of L-Dopa to DA and NE (Geyer et al., 1972) influenced the acquisition of avoidance responding. The effects of L-Dopa on activity level would appear to be responsible for the significant number of inter-trial crossovers produced. In the sense that inter-trial crossovers are an indication of activity level, the results of the present study due to the administration of L-Dopa coincide well with studies which report an enhancement of performance on a conditioned avoidance task.

In conjunction with a heightened activity level as displayed by the L-Dopa group, the effects of aversive stimuli may have served to impair the learning of an active avoidance task. The fact that inter-trial crossovers were discouraged appears to have complicated the learning task; this is true since repeated errors during the inter-trial interval were immediately followed by foot shock. A higher incidence of foot shock for those animals that had a greater tendency to crossover between trials might have conflicted with acquisition. Because foot shock followed the correct motor response when an animal produced an inter-trial interval crossover, it is possible that the overall number of avoidances were decreased.

Within the parameters of the present study the effects of 5-HTP on inter-trial crossovers are difficult to explain. The significant decrease in inter-trial crossovers during the

first two days of training might reflect a possible release of catecholamines as a result of the initial administration of 5-HTP. In view of the fact that 5-HTP results in a higher threshold for foot shock (Tenen, 1967), it is not surprising that the 5-HTP group did not differ from Controls. Relatively high foot shock levels have been reported to have little effect upon acquisition (Essman, 1971).

A possible explanation of the effect of 5-HTP can be found in a study of the effects of microelectrophoretically administered 5-HT on the neurons of the lateral geniculate body in unanaesthetized (decerebrate) cats. The depressant action of 5-HT on the lateral geniculate neurons was found to be dose dependent. Low injecting currents easily depressed the orthodromic firing by light stimulation and nerve stimulation via acetylcholine. Higher injecting currents had a greater effect on the depression of both antidromic and orthodromic firing and spontaneous activity than did DA and NE (Tebecis & Di Maria, 1972). Such results provide evidence that tryptamine derivatives may have a role in blocking the release of the excitatory transmitter from optic nerve terminals, or preventing its availability to lateral geniculate neurons. Histochemical evidence suggests that the pathway for tryptaminergic afferent fibers to the lateral geniculate neurons originates in the brain stem. In view of the fact that the stimulation of the mesencephalic reticular formation depresses activity of the lateral geniculate neurons (Tebecis & Di Maria, 1972), it would seem reasonable to suggest that

increased regional concentrations of 5-HT can serve to inhibit the acquisition of a visual task. Nevertheless, it would appear that a more sensitive test than the present methodology permits is necessary in order to assess the effects of 5-HTP on acquisition.

The assumptions of a nonadditive model for the analysis of variance suggest a subject x treatment interaction (Hays, 1963; Edwards, 1968; Myers, 1966). Implications of such interactive effects indicate that the daily administration of 5-HTP and L-Dopa did not produce effects that were constant across the training sessions. The possibility exists that the effects of metabolites of L-Dopa and 5-HTP varied within subjects as a function of the daily drug administration.

It has been demonstrated that brain levels of DA and 5-HT co-vary as a function of the particular precursor administered as well as the quantity administered (Everett & Borcherding, 1970; Okada et al., 1972; McGeer et al., 1963a) and that brain concentrations of 5-HT and NE are increased as a result of forced mobility (Elo & Tirri, 1972) and foot shock (Bliss, Ailion & Zwanziger, 1968; Thierry, Javoy, Glowinski & Kety, 1968). The effect of 5-HTP on the catecholamines and of L-Dopa on 5-HT, in addition to the alteration of 5-HT and NE concentrations by active avoidance or escape of foot shock, appear to have confounded the present results.

Though the first six days of training resulted in a significant drug effect, it was not possible to determine the

particular drug affecting acquisition. For this reason future studies of the effects of amine precursors might include a study of the interactive effects of these amines by the administration of both 5-HTP and L-Dopa in varying quantities. Utilizing such a methodology it might be possible to determine which drug has the greater effect upon acquisition, if any. However, since the decarboxylase activity of 5-HTP and L-Dopa are in constant ratio to each other in brain tissue (Friede, 1966) and the decarboxylation of these amines is mediated by the same enzyme (Cooper, Bloom & Roth, 1970; Carlsson, 1964), it is difficult to attempt an analysis of behavioral effects without first establishing correlations between variations in regional concentrations and specific behavior. The establishment of variations in regional concentrations of 5-HT and DA is most important when one attempts to examine central and/or peripheral effects of such amines upon specific behavior.

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APPENDIX A

STATISTICAL TABLES

TABLE 1

Analysis of variance: latency data for 13 days of training.

Source	df	SS	EMS	F
Between				
Drug	2	16.60	8.30	1.48
Error	21	117.65	5.60	
Within				
Trials	12	994.93	82.91	30.94***
Trials x drug	24	38.06	1.59	0.59
Error	252	674.95	2.68	

***$P < .001$

TABLE 2

Analysis of variance: latency data for the first 6 days of training.

Source	df	SS	EMS	F
Between				
Drug	2	25.29	12.65	4.44*
Error	21	59.81	2.85	
Within				
Trials	5	229.76	45.95	48.37***
Trials x drug	10	15.40	1.54	1.62
Error	105	99.79	0.95	

*$p < .05$

***$p < .001$

TABLE 3

Analysis of variance: frequency of avoidance for 13 days of training.

Source	df	SS	EMS	F
Between				
Drug	2	91.41	45.71	0.74
Error	21	1,305.36	62.16	
Within				
Trials	12	8,724.53	727.04	129.37***
Trials x drug	24	215.92	8.99	1.60*
Error	252	1,415.40	5.62	

*$P < .05$

***$P < .001$

TABLE 4

Analysis of variance: frequency of avoidance for the first 6 days of training

Source	df	SS	EMS	F
Between				
Drug	2	60.43	30.22	0.75
Error	21	847.88	40.38	
Within				
Trials	5	836.89	167.38	56.36***
Trials x drug	10	191.07	19.11	5.94***
Error	105	338.37	3.22	

***$P < .001$

TABLE 5

Analysis of variance: frequency of inter-trial crossovers for 13 days of training.

Source	df	SS	EMS	F
Between				
Drug	2	42.35	21.18	17.72***
Error	21	25.10	1.20	
Within				
Trials	12	16.26	1.36	2.26**
Trials x drug	24	20.57	0.86	1.43
Error	252	150.02	0.60	

**$P < .01$

***$P < .001$

TABLE 6

Duncan New Multiple Range Test: comparison of the mean number of inter-trial crossovers for each group for the first day of training.

Means	Control .125	L-Dopa 1.38	5-HTP 1.75	Shortest Significant Ranges
Control = .13		1.26**	1.63**	R-2 = 1.2488
L-Dopa = 1.38			.37	R-3 = 1.2994

**$\underline{P} < .005$

TABLE 7

Duncan New Multiple Range Test: comparison of the mean number of inter-trial crossovers for each group for the second day of training.

Means	Control .38	L-Dopa 1.25	5-HTP 1.25	Shortest Significant Ranges
Control = .38		.87*	.87*	R-2 = .6490
L-Dopa = 1.25			0.00	R-3 = .6813

*$P < .05$

APPENDIX B

TEST DATA

MEAN DAILY LATENCIES

TABLE 8

Mean daily latencies for each subject

L-Dopa Group

Days	1	2	3	4	5	6	7	8
1	13.14	11.69	12.95	12.46	11.23	11.23	11.13	12.79
2	10.61	10.81	10.48	9.16	12.51	10.22	10.32	10.53
3	10.83	10.13	9.65	8.22	10.61	8.13	7.90	10.29
4	8.76	9.38	7.86	6.38	7.94	8.38	7.14	9.97
5	8.09	8.42	8.86	6.31	9.74	9.35	3.27	8.56
6	8.39	8.69	8.70	8.68	7.28	8.80	5.23	8.53
7	7.46	7.80	9.72	6.45	7.03	7.92	5.32	8.66
8	6.95	8.05	6.41	5.27	5.36	7.28	5.42	8.15
9	6.67	5.92	8.22	5.19	6.02	6.38	5.70	8.22
10	8.91	7.78	7.05	6.27	6.73	6.89	5.84	6.59
11	8.63	6.39	5.25	4.39	4.84	6.21	5.09	7.17
12	6.47	6.33	6.26	5.78	5.79	5.84	5.42	7.97
13	6.20	5.45	5.37	6.16	5.90	5.94	6.08	7.22

TABLE 9

Mean daily latencies for each subject

5-HTP Group

Days	1	2	3	4	5	6	7	8
1	11.31	10.34	10.60	10.55	11.53	10.88	11.15	10.44
2	10.77	10.70	11.86	11.48	10.91	9.85	10.95	9.28
3	10.76	11.32	9.13	10.00	11.85	8.80	10.52	8.81
4	10.16	10.37	9.03	10.84	10.46	10.73	9.92	7.36
5	8.74	8.31	8.56	10.05	9.43	9.59	9.94	7.66
6	9.24	8.48	7.33	8.70	9.78	8.79	10.57	6.96
7	9.20	8.84	7.85	8.22	8.95	7.68	8.92	4.81
8	7.74	6.38	8.57	8.03	5.60	5.74	6.36	5.39
9	7.10	7.78	7.71	8.11	7.29	6.77	7.40	5.90
10	7.43	7.17	7.56	7.60	6.90	8.05	7.69	5.53
11	6.23	6.62	7.57	6.77	7.33	6.06	7.03	6.35
12	6.93	6.43	7.17	6.83	6.50	5.43	6.18	6.23
13	7.76	7.09	5.28	5.90	5.88	6.69	7.45	6.54

TABLE 10

Mean daily latencies for each subject

Control Group

Days	1	2	3	4	5	6	7	8
1	13.00	12.81	12.42	12.98	12.28	12.49	13.64	11.69
2	12.94	10.87	11.71	10.38	10.96	11.21	11.49	11.16
3	11.75	10.25	10.59	10.11	10.37	10.45	10.64	10.36
4	9.30	8.88	10.20	8.37	11.24	10.73	9.83	7.09
5	9.04	8.97	8.09	6.39	9.30	9.24	9.29	7.47
6	9.82	9.35	6.79	7.03	9.22	8.94	9.63	8.12
7	9.03	7.84	5.49	7.24	7.82	6.71	6.74	6.16
8	9.18	7.71	6.08	4.63	6.44	7.66	7.60	6.93
9	8.42	9.14	7.98	7.37	5.85	7.63	7.91	6.02
10	8.22	6.15	6.40	4.49	6.83	6.43	7.37	6.38
11	7.92	6.41	6.69	5.63	5.84	5.92	4.73	6.64
12	7.51	6.62	7.05	6.71	5.31	5.96	6.31	6.98
13	6.26	6.37	6.43	7.08	6.57	6.29	7.42	6.09